Sub D1

1. **(Thrice Amended)** A computer-aided method of docking a ligand to a protein having a binding site, said method comprising:

performing a pre-docking conformational search to generate multiple conformations of the ligand in solution;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one conformation of the multiple conformations of the ligand in solution to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and

optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

C1

C2

Sub D2

2. **(Amended)** The method of claim 1, wherein said performing the pre-docking conformational search comprises creating a database of the multiple conformations of the ligand in solution and storing said three-dimensional database for subsequent use by said matching.

3. **(Amended)** The method of claim 2, wherein said database of the multiple conformations of the ligand in solution comprises a conformational database of a combinatorial library.

C3

Sub D3

4. **(Thrice Amended)** The method of claim 1, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of conformations of the molecule;

minimizing a strain of each conformation of the plurality of conformations;

using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple conformations of the ligand in solution.

C4 Sub D4

7. **(Twice Amended)** The method of claim 1, wherein said matching comprises:

matching atoms of the at least one conformation of the ligand in solution to appropriate hot spots of the protein by positioning the at least one conformation of the ligand in solution as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one conformation of the molecule in solution into the binding site of the protein.

8. **(Amended)** The method of claim 7, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{i,j} |H_i - RA_j - T|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one conformation of the ligand in solution;

H_i = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one conformation of the ligand in solution;

R = a 3x3 rotation matrix; and

T = a translation vector.

9. **(Thrice Amended)** The method of claim 1, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

10. **(Thrice Amended)** The method of claim 9, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

11. **(Thrice Amended)** A computer-aided system for docking a ligand to a protein having a binding site, said system comprising:

means for performing a pre-docking conformational search to generate multiple conformations of the ligand in solution;

means for generating a binding site image of the protein, said binding site image comprising multiple hot spots;

means for matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple conformations of the ligand in solution to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and

means for optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

12. **(Amended)** The system of claim 11, wherein said means for performing the pre-docking conformational search comprises means for creating a database of the multiple conformations of the ligand in solution and for storing said three-dimensional database for subsequent use by said matching.

13. The system of claim 12, wherein said database of the multiple conformations of the ligand in solution comprises a conformational database of a combinatorial library.

14. **(Thrice Amended)** The system of claim 11, wherein said means for performing the pre-docking conformational search comprises:

means for randomly generating a plurality of conformations of the ligand;

means for minimizing a strain of each conformation of the plurality of conformations;

means for using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

means for clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple conformations of the ligand in solution.

17. **(Twice Amended)** The system of claim 11, wherein said means for matching comprises:

means for matching atoms of the at least one conformation of the ligand in solution to appropriate hot spots of the protein by positioning the at least one conformation of the ligand in solution as a rigid body into the binding site image;

means for defining a match, said match determining a unique rigid body transformation; and

means for using the unique rigid body transformation to place the at least one conformation of the ligand in solution into the binding site of the protein.

18. **(Thrice Amended)** The system of claim 17, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{n} |H_j - RA_j - T|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one conformation of the ligand in solution;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one conformation of the ligand in solution;

R = a 3x3 rotation matrix; and

T = a translation vector.

19. **(Thrice Amended)** The system of claim 11, wherein multiple positions of the ligand are obtained, and said means for optimizing comprises :

means for eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

means for ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, means for clustering the positions of the ligand and selecting a top number n of positions; and

means for optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

20. **(Thrice Amended)** The system of claim 19, wherein said means for optimizing comprises means for optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

21. **(Thrice Amended)** At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of docking a ligand to a protein having a binding site, said method comprising:

performing a pre-docking conformational search to generate multiple conformations of the ligand in solution;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one conformation of the multiple conformations of the ligand in solution to obtain at least one position of the ligand relative to the protein in a protein-ligand complex; and

optimizing the at least one position while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed.

22. **(Amended)** The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search comprises creating a database of the multiple conformations of the ligand in solution and storing said three-dimensional database for subsequent use by said matching.

23. **(Amended)** The at least one program storage device of claim 22, wherein said database of the multiple conformations of the ligand in solution comprises a conformational database of a combinatorial library.

24. **(Thrice Amended)** ~~The at least one program storage device of claim 21,~~ wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of conformations of the ligand;

minimizing a strain and a solvent accessible surface area of each conformation of the plurality of conformations;

using the strain of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple conformations of the ligand in solution.

27. **(Twice Amended)** The at least one program storage device of claim 21, wherein said matching comprises:

matching atoms of the at least one conformation of the ligand in solution to appropriate hot spots of the protein by positioning the at least one conformation of the ligand in solution as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one conformation of the ligand in solution into the binding site of the protein.

28. **(Thrice Amended)** The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one conformation of the ligand in solution;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one conformation of the ligand in solution;

R = a 3x3 rotation matrix; and

T = a translation vector.

29. **(Thrice Amended)** The at least one program storage device of claim 21, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

30. **(Thrice Amended)** The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

REMARKS